Sunday Akintoye
NIH/NIDCR/DIR, Building 10, 1N-113
10 Center Drive, MSC 1190
Bethesda, MD 20892-1190

ATTN:
PHONE: 301-594-1645
FAX: sakintoye@dir.nidcr.nih.g

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Craniofacial Growth in Short Children Born Small for Gestational Age: Effect of Growth Hormone Treatment

R. Van Erum[1*], M. Mulier[1], C. Carels[1], G.Verbeke[2], and F. de Zegher[3]

[1]School of Dentistry, Department of Orthodontics, University Hospital St. Rafaël, Capucijnenvoer 7, 3000 Leuven, Belgium; [2]Biostatistical Centre for Clinical Trials, University of Leuven, Belgium; [3]Department of Pediatrics, University of Leuven, Belgium; *to whom correspondence should be addressed

Abstract. The effects of growth hormone (GH) therapy in children have yet to be completely catalogued. In the present study, the effect of high-dose GH treatment on craniofacial growth was evaluated once yearly in 21 pre-pubertal, non-GH-deficient children born small for gestational age. These children were randomly allocated to be either untreated or treated with GH at a daily subcutaneous dose of 0.2 or 0.3 IU/kg for 2 yrs. The group consisted of 12 girls and 9 boys with a mean age of 5.1 yr (range, 2 to 8 yr), bone age of 3.4 yr, and height SDS of -3.6. At the start of the study, all children showed an overall delay of craniofacial growth. This cohort of short children born small for gestational age showed a small SNB angle and a large ANB angle; all other angular measurements were within normal range. GH treatment accelerated growth in several craniofacial components, especially the posterior total facial height, the cranial base length, and the overall mandibular length. The increase of the mandibular length increased the SNB angle; no other angular measurements were affected. Age at start of treatment differently influenced the increase in posterior and total cranial base length, the increase in mandibular corpus length, and the position of the mandible in relation to the cranial base. Although GH treatment for 2 yrs led to a craniofacial growth acceleration, the position of the mandible in relation to the cranial base and the craniofacial size in lateral aspect were not normalized in the majority of the GH-treated children. No signs of disproportional growth were evidenced after 2 yrs of high-dose GH treatment. In conclusion, short pre-pubertal SGA children display an overall delay of linear craniofacial growth and a retrognathic mandible. High-dose GH treatment over 2 yrs leads to craniofacial catch-up growth, which is pronounced in regions where interstitial cartilage is involved and results in a less convex face in profile.

Key words: intra-uterine growth retardation, cephalometry, longitudinal study.

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Introduction

Normal fetal growth is dependent on a balance between the natural growth potential of the fetus and the fetal environment, the latter being controlled by placental and maternal factors. In many children born small for gestational age (SGA), no underlying cause can be found (Heinrich, 1992). The endocrine status of a fetus with idiopathic intra-uterine growth retardation is reminiscent of a state of GH resistance (de Zegher *et al.*, 1990; Lassarre *et al.*, 1991; Giudice *et al.*, 1995). Most SGA children (nearly 90%) show catch-up growth during the first two years of life (Hokken-Koelega *et al.*, 1995; Karlberg and Albertsson-Wikland, 1995). Those who do not may enter puberty early and present a reduced final height (Fitzhardinge and Inwood, 1989). An increased incidence of GH deficiency or an abnormality in the GH secretory pattern has been observed in these children (Albertsson-Wikland, 1989). In the attempt to normalize the short stature of these children, GH treatment has been explored for many years. In the '60s and '70s, GH administration with low frequency (Tanner *et al.*, 1971; Grunt *et al.*, 1972) or in low-substitution doses (Foley *et al.*, 1974; Lanes *et al.*, 1979) was used but without satisfactory effect. More recently, a few reports have shown an increase in growth velocity of SGA children treated with high-dose GH (Stanhope *et al.*, 1991; Chatelain *et al.*, 1994).

Reports in the literature concerning the craniofacial development in SGA children are few; in non-GH-deficient SGA children, facial growth retardation resembles that in children with pituitary deficiency (Spiegel *et al.*, 1971). Although an association between craniofacial and somatic development has been clearly established by longitudinal growth studies (Nanda, 1955; Björk and Helm, 1967; Baughan *et al.*, 1979), and the effect of GH on longitudinal bone growth is well-documented (Isaksson *et al.*, 1987), the effect of GH on the individual craniofacial bony components is poorly understood. Cephalometric studies in children with GH deficiency have shown small anterior and posterior cranial base dimensions and small mandibular sizes (Spiegel *et al.*, 1971; Poole *et al.*, 1982). Further, a small posterior facial and mandibular height has been demonstrated (Pirinen *et al.*, 1994).

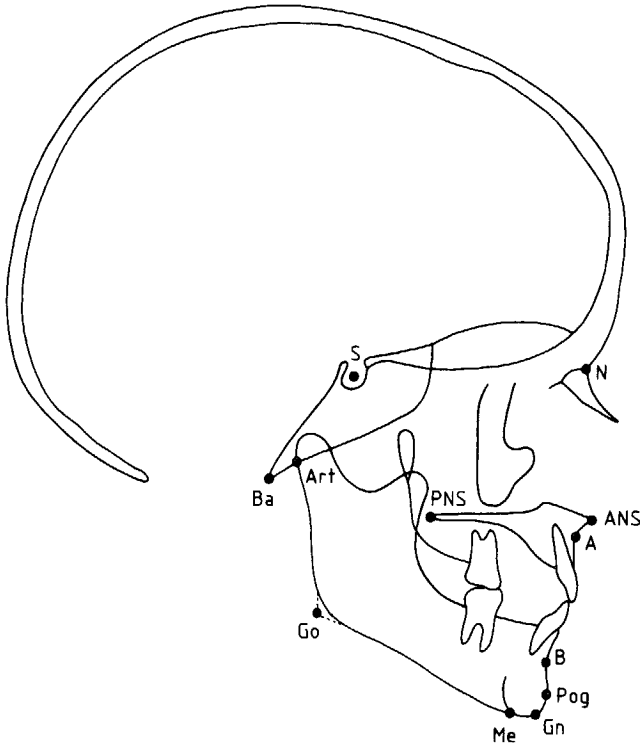

Figure 1. Cephalometric landmarks.

The influence of conventional GH therapy on craniofacial growth has been studied in children with GH deficiency: substitution treatment was found to increase mandibular length and lower face height, while the cranial base length showed minimal changes (Poole *et al.*, 1982). When higher doses are given to achieve a definite growth-promoting effect (Stanhope *et al.*, 1991; Chatelain *et al.*, 1994), there may be a risk of inducing acromegalic effects.

The effect of a relatively high dose of growth hormone on craniofacial growth was recently studied in girls with Turner's syndrome. The 2 yrs of GH treatment in these patients resulted in an increase of mandibular length, mainly due to vertical growth of the ramus; the initially posteriorly rotated mandible showed an anterior rotation (Rongen-Westerlaken *et al.*, 1993).

A randomized, controlled, explorative study is presented here to investigate the effect of a daily high dose of GH over 2 yrs on craniofacial growth in SGA children.

Materials and methods

Study population

The studied children formed a subpopulation followed at our University Hospital in Leuven within an open-labeled multicenter clinical trial, in which the overall growth-promoting effect of GH treatment in short SGA children was examined over 2 yrs (de Zegher *et al.*, 1996a). Three parallel groups were recruited by means of a weighted randomization (fewer controls than treated children). One group was an untreated control group (n = 4), and two groups were treated with daily subcutaneous injections of recombinant human GH (Genotropin; Pharmacia, Stockholm, Sweden) at a dose of either 0.2 IU/kg (n = 9) or 0.3 IU/kg (n = 8). Treatment was continued for 24 mos, and the dosage was adjusted every 6 mos.

Inclusion criteria were: weight and/or length at birth below -2 SD for gestational age; height standard deviation score (SDS) for age less than -2.5; height velocity less than +1 SDS (to exclude children presenting spontaneous catch-up growth); age between 2 and 8 yrs at the start of the study; and serum GH concentration of at least 10 µg/L, spontaneously, after exercise, glucagon, or insulin tolerance test. Exclusion criteria were: endocrine disorders, Turner's or Down's syndrome, previous or ongoing radiotherapy or anabolic steroid therapy, and severe chronic disease or mental retardation. The group of 21 children consisted of 12 girls and nine boys. The mean age at start was 5.1 yr, the mean (SD) height for chronological age was -3.6 (0.7) SDS, and the mean bone age (Tanner-Whitehouse II method) was 3.4 (1.6) yr.

The study protocol was approved by the Ethics Committee of the Medical School, University of Leuven. Before study initiation, written informed consent was obtained from at least one of the parents or a legal representative of each child.

After 2 yrs, catch-up growth was observed in all of the treated and in none of the untreated children. GH treatment resulted in a near-doubling of growth velocity and of weight gain, and a mean height increment of more than 2 SDS. Although GH treatment accelerated bone maturation, the final height prognosis was improved (de Zegher *et al.*, 1996a).

Cephalometric analysis

At the onset of the study and at yearly intervals thereafter, lateral cephalometric radiographs were taken under standardized conditions with the teeth in maximal occlusion. To evaluate craniofacial growth, we traced the lateral headplates and identified 12 cephalometric landmarks (Fig. 1). These landmarks were digitized, and 12 linear and 7 angular measurements (Table 1) were computed by means of the computer program Quick Ceph™ (Orthodontic Processing, Chula Vista, CA). All radiographs were digitized twice and independently by the first two authors. No significant inter- or intra-observer error was found, so the arithmetic average of the four observations was used for statistical analysis.

The control sample used for comparison of the craniofacial sizes of the children at the start and after GH therapy or untreated period with those of a normal population consisted of the children of the Broadbent series, based on a North American population of Caucasian origin (Broadbent *et al.*, 1975), the so-called Bolton Standards of dentofacial developmental growth. Eight of the 12 observed linear variables and 5 of the 7 angular variables were found in the standard measurements given in the Bolton series (Table 1). We used this historical control group because it is the only one with norms for such young children (youngest child is 2 yrs old). Because of a different cephalometric technique, which produces different percentages of enlargement in the Bolton Standards, a correction for enlargement was performed for all linear measurements.

Statistical analyses

The repeated cephalometric measurements, at the start of the

Table 1. Linear and angular craniofacial measurements

Linear	Abbreviation	Cephalometric Landmarks	Angular	Abbreviation	Cephalometric Landmarks
Anterior cranial base length[a]	ACB	N - S	Saddle angle[a]	SA	N - S - Art
Posterior cranial base length[a]	PCB	S - Ba	Gonial angle	GA	Art - Go - Me
Total cranial base length	TCB	N - Ba	Mandibular plane angle[a]	MPA	S-N - Go-Gn
Upper anterior facial height[a]	UAFH	N - ANS	Position of maxilla[a]	SNA	S - N - A
Upper posterior facial height	UPFH	S - PNS	Position of mandible[a]	SNB	S - N - B
Lower anterior facial height[a]	LAFH	ANS - Me	Maxilla/Mandible[a]	ANB	A - N - B
Anterior total facial height[a]	ATFH	N - Me	Posterior position of mandible	PPMand	S-N - Art-Go
Posterior total facial height	PTFH	S - Go			
Maxillar length[a]	MaxL	ANS - PNS			
Mandibular ramus length[a]	MandRL	Art - Go			
Mandibular corpus length[a]	MandCL	Go - Pog			
Overall mandibular length	OMandL	Art - Pog			

[a] For these variables, norms are given in Broadbent *et al.*, 1975.

study and after one and two years, respectively, were statistically analyzed. The dependence of the one- and two-year changes on GH dose, sex, and age at first measurement was investigated by means of a multivariate normal model that corrected for possible initial differences with respect to each of these factors. Calculations were carried out with the SAS procedure MIXED (SAS Institute Inc., 1992). To evaluate the craniofacial growth in the children of the different observation groups at the start of the study and after 2 yrs in comparison with a normal population, we calculated percentiles. For each child, the probability that a particular craniofacial measurement differs from that in a normal individual was determined. The arithmetic average of these probabilities was calculated and tested for significance.

Results

Linear

At the start of the study, all the linear craniofacial sizes in the entire group were extremely short relative to the Bolton Standards, since, for all variables, the mean of the percentile calculations was smaller than 0.5 ($p < 0.001$, and $p < 0.05$ for the lower anterior facial height). Despite this, there is a high variability (high SD) among the SGA children, especially for the anterior and posterior total facial height, for the mandibular corpus length, and for the overall mandibular length (Table 2).

After 2 yrs, GH treatment was found to have a growth-accelerating effect in several craniofacial components. The linear craniofacial variables increased more in the treated groups than in the untreated group. In both treatment groups, all the linear craniofacial variables, except for maxillary length and the lower anterior facial height, showed significant catch-up growth that was not observed in the untreated group. All the effects were non-linear in time (Figs. 2, 3).

The posterior total facial height (Fig. 2; upper panel, left) evolved differently ($p < 0.05$) in the two GH dose groups. The highest GH dose evoked the most pronounced

Table 2. Mean (± SD) for the linear and angular craniofacial variables

Linear	Mean ± SD (mm) at Start			Mean ± SD (mm) after 2 yr		
	Dose 0 n = 4	Dose 0.2 n = 9	Dose 0.3 (IU/kg/d) n = 8	Dose 0 n = 4	Dose 0.2 n = 9	Dose 0.3 (IU/kg/d) n = 8
ACB	59.5 ± 2.6	61.2 ± 2.2	59.2 ± 2.7	61.4 ± 3.1	64.3 ± 2.8	63.7 ± 1.6
PCB	36.2 ± 2.2	36.3 ± 3.4	35.5 ± 4.6	37.0 ± 4.0	40.7 ± 3.0	42.4 ± 2.1
TCB	89.4 ± 2.1	88.6 ± 3.6	87.9 ± 5.0	91.2 ± 3.6	95.4 ± 3.4	95.5 ± 2.4
UAFH	37.4 ± 1.1	37.6 ± 2.9	38.9 ± 4.4	41.0 ± 0.5	45.3 ± 4.1	44.7 ± 3.1
UPFH	57.3 ± 2.5	55.3 ± 3.0	55.6 ± 4.5	60.8 ± 2.2	62.5 ± 4.5	62.8 ± 3.0
LAFH	55.0 ± 2.1	58.8 ± 3.9	55.1 ± 3.5	55.9 ± 2.1	61.4 ± 4.4	60.2 ± 3.5
ATFH	90.8 ± 1.8	93.5 ± 6.7	91.9 ± 5.3	95.4 ± 2.3	104.2 ± 9.0	103.5 ± 4.2
PTFH	52.4 ± 8.3	52.2 ± 4.0	52.0 ± 6.4	55.1 ± 10.0	59.8 ± 5.2	62.8 ± 5.2
MaxL	43.9 ± 3.1	45.7 ± 2.1	42.7 ± 3.7	46.7 ± 3.7	49.7 ± 2.6	48.0 ± 3.7
MandRL	32.4 ± 6.5	30.7 ± 2.7	30.5 ± 5.0	34.0 ± 6.5	34.4 ± 3.0	37.0 ± 3.9
MandCL	55.9 ± 5.3	56.1 ± 4.6	55.6 ± 4.1	60.2 ± 6.5	62.1 ± 4.7	63.8 ± 3.1
OMandL	79.4 ± 7.8	79.1 ± 4.9	76.6 ± 7.2	84.0 ± 8.0	86.3 ± 5.1	87.8 ± 5.4
Angular	**Mean ± SD (°) at start**			**Mean ± SD (°) after 2 yr**		
	Dose 0 n = 4	Dose 0.2 n = 9	Dose 0.3 (IU/kg/d) n = 8	Dose 0 n = 4	Dose 0.2 n = 9	Dose 0.3 (IU/kg/d) n = 8
SA	129.6 ± 4.2	118.0 ± 10.5	121.7 ± 4.5	131.3 ± 6.1	120.7 ± 5.4	122.7 ± 3.5
GA	133.2 ± 6.0	136.0 ± 5.9	131.2 ± 5.7	131.6 ± 6.1	133.8 ± 5.2	128.9 ± 6.4
MPA	31.1 ± 1.9	37.7 ± 4.1	34.3 ± 5.3	31.9 ± 3.1	38.8 ± 4.3	35.6 ± 4.7
SNA	81.8 ± 5.9	84.1 ± 2.7	80.2 ± 4.3	80.1 ± 7.3	82.8 ± 2.8	80.8 ± 3.6
SNB	73.5 ± 4.9	76.5 ± 2.6	73.9 ± 3.1	75.7 ± 6.5	77.9 ± 1.9	77.3 ± 2.3
ANB	6.3 ± 2.3	7.6 ± 3.3	6.3 ± 1.7	4.4 ± 0.9	4.9 ± 2.1	3.5 ± 1.2
PPMand	85.5 ± 3.4	83.9 ± 3.7	89.2 ± 4.0	87.0 ± 6.1	86.4 ± 4.4	87.3 ± 2.9

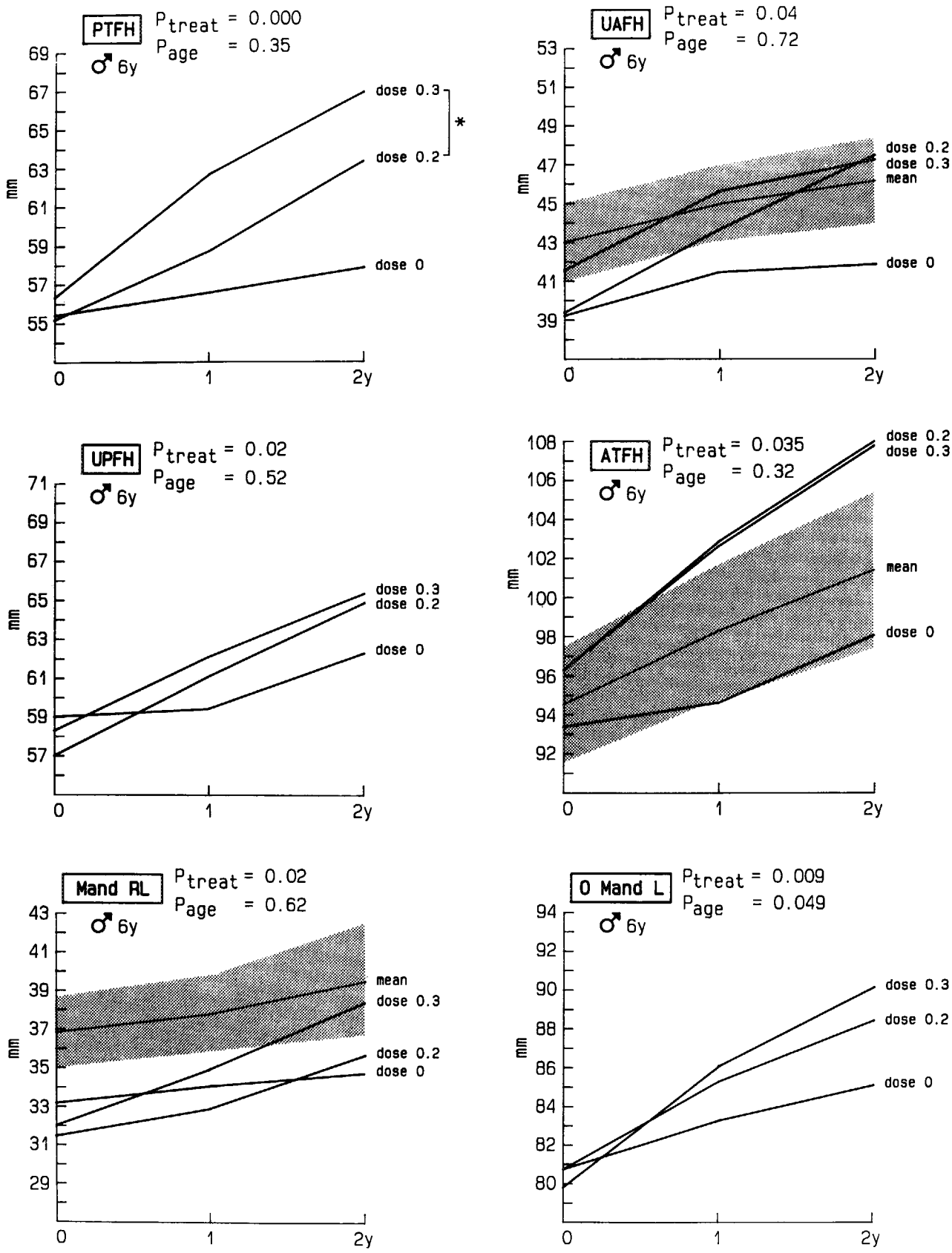

Figure 2. Predicted average evolution of several **linear** craniofacial variables for boys at the age of 6 yr for the three dose groups over a period of 2 yrs. All variables on which GH treatment has a significant (P_{treat}) growth-promoting effect are graphically demonstrated, presuming a mean age of 6 yrs.

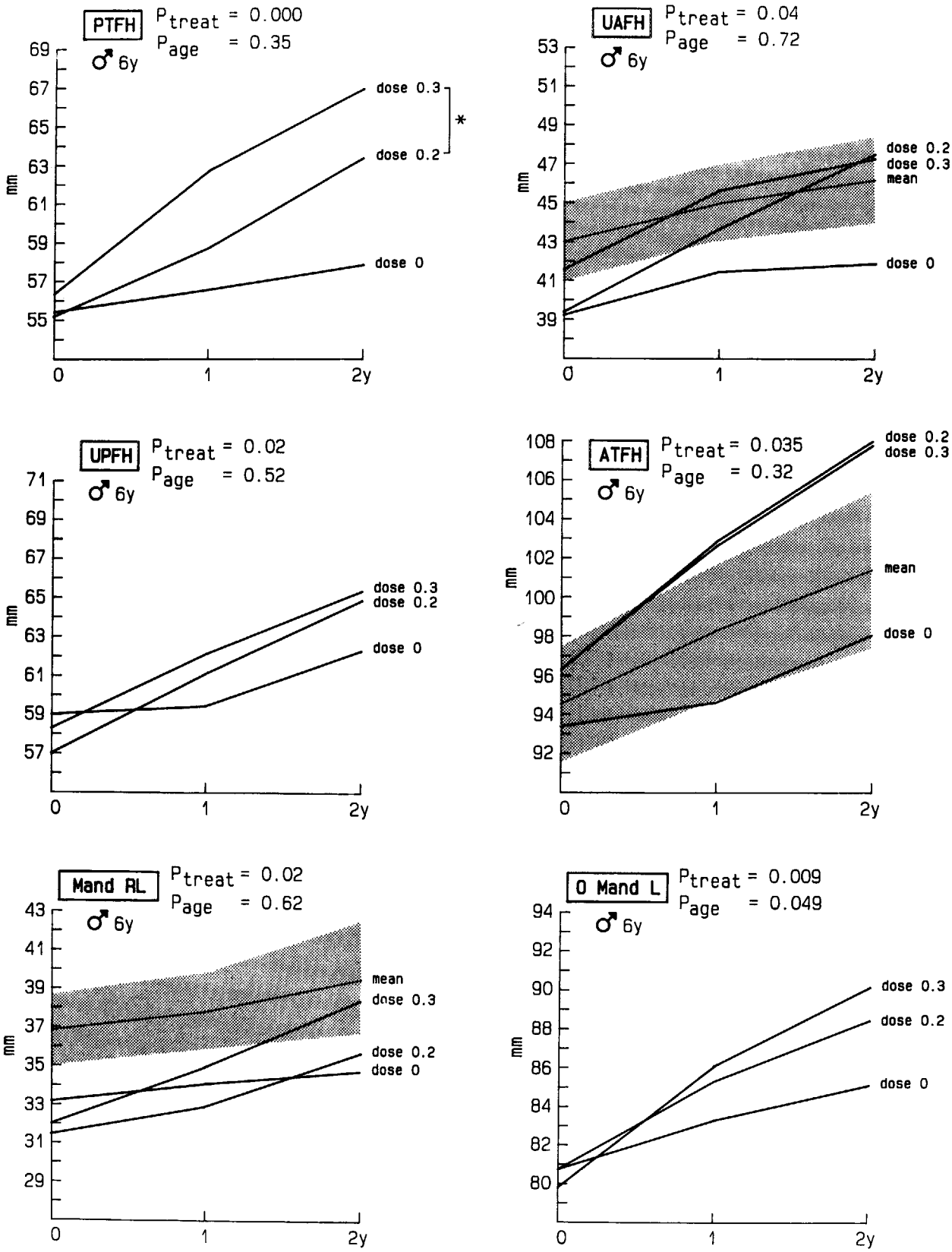

Figure 3. For the variables where the age at the start of the treatment has a significant effect (P_{age}) on the growth evolution (Fig. 3), predictive graphs for boys starting treatment at age 3 yrs are also given (Fig. 3, left panels). Normal values are indicated (mean ± 1 SD) when available. Refer to Table 1 for abbreviations.

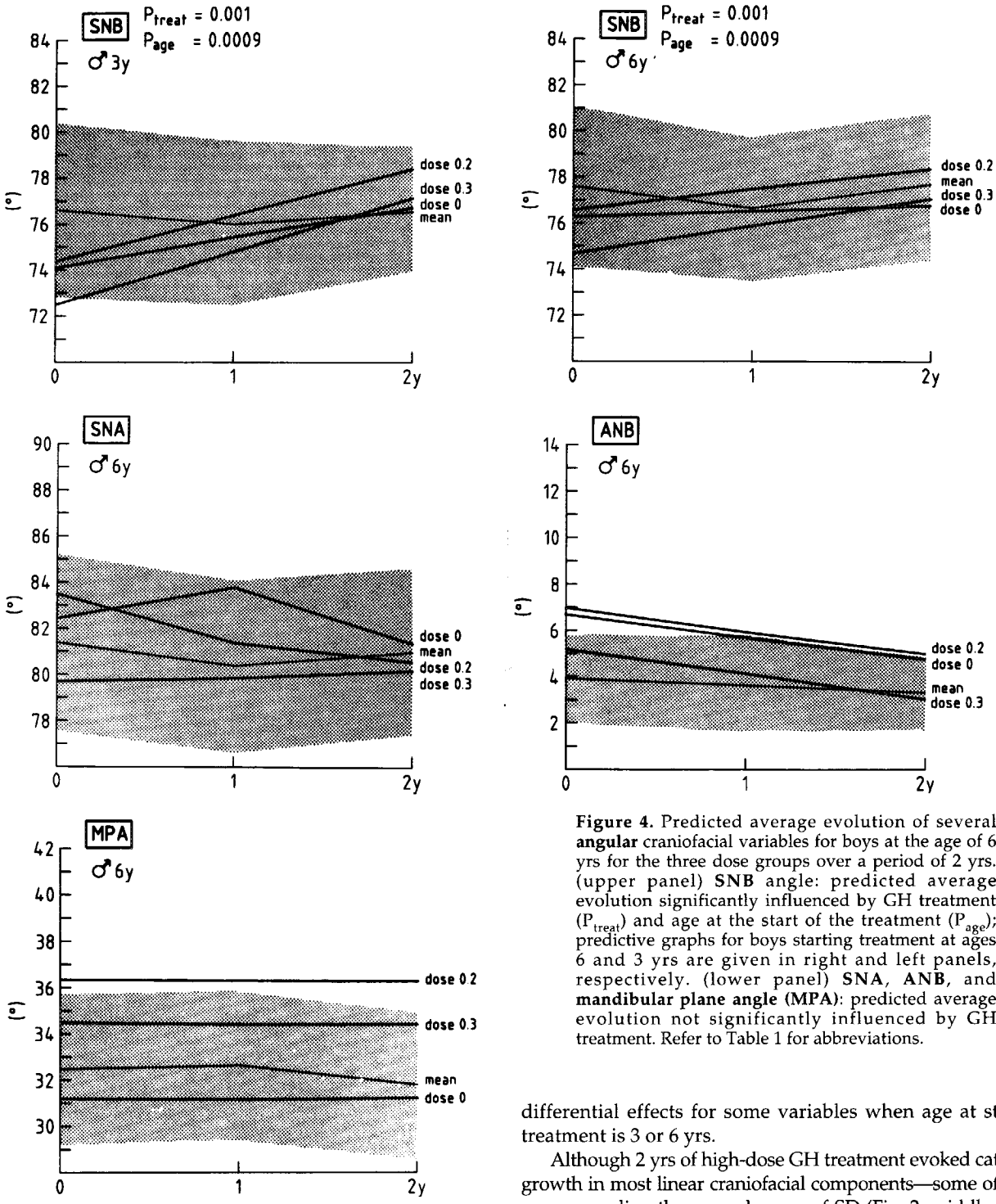

Figure 4. Predicted average evolution of several **angular** craniofacial variables for boys at the age of 6 yrs for the three dose groups over a period of 2 yrs. (upper panel) **SNB** angle: predicted average evolution significantly influenced by GH treatment (P_{treat}) and age at the start of the treatment (P_{age}); predictive graphs for boys starting treatment at ages 6 and 3 yrs are given in right and left panels, respectively. (lower panel) **SNA**, **ANB**, and **mandibular plane angle (MPA)**: predicted average evolution not significantly influenced by GH treatment. Refer to Table 1 for abbreviations.

growth response.

For the total cranial base length (Fig. 3; upper panels), the mandibular corpus length (Fig. 3; middle panels), and the posterior cranial base length (Fig. 3; lower panels), the growth change was dependent on the age at the start of GH administration: the younger the age, the more pronounced the growth-promoting effect on these variables. Therefore, predictive data are calculated to demonstrate the differential effects for some variables when age at start of treatment is 3 or 6 yrs.

Although 2 yrs of high-dose GH treatment evoked catch-up growth in most linear craniofacial components—some of them even exceeding the normal range of SD (Fig. 2, middle panel, right; Fig. 3, lower panel, left)—the majority of the variables in the treated children failed to normalize. Indeed, all the linear craniofacial dimensions in the treated children remained small in comparison with the Bolton Standards ($p < 0.01$), except for the lower anterior and total anterior facial height.

Angular

At the start of the study, the angular measurements did not

differ consistently from the norms, except for a smaller SNB angle ($p < 0.001$) and a wider ANB angle ($p < 0.01$). There is also a high variability concerning angular craniofacial measurements in SGA children (Table 2).

After 2 yrs, GH treatment was found to have an increasing effect on the SNB angle (Fig. 4, upper panel), although the normal position in relation to the cranial base was not reached in either of the treatment groups ($p < 0.01$). This increase in SNB angle was dependent on the age at start of GH administration; the younger the age at start of GH treatment, the more pronounced the increasing effect on this variable (Fig. 4, upper panel). None of the other angular measurements showed significant differences between treated and untreated groups (Fig. 4, lower panel).

Discussion

This study demonstrates that growth retardation in SGA children with failed catch-up growth concerns not only their statural height but also their craniofacial development, as is the case with children with GH deficiency (Spiegel *et al.*, 1971).

The results in the present study show that angular facial proportions are not affected but that linear dimensions are small in short SGA children when compared with age-matched controls; the anterior cranial base length was most shortened and the anterior facial height the least. There appears to be some resemblance in craniofacial growth retardation between SGA and GH-deficient children. However, GH-deficient children have a normal maxillary length, in contrast to SGA children (Poole *et al.*, 1982).

Two years of high-dose GH treatment lead to overall craniofacial growth acceleration, and it seems that GH is most effective in those regions where cartilage-mediated growth occurs and in regions adapting for this cartilage growth. The highest growth increments are found at the spheno-occipital synchondrosis, the mandibular condyle, and the dento-alveolar region. The growth increment was most marked for the posterior facial height, which reflects growth both from the spheno-occipital synchondrosis in the posterior part of the cranial base and from the mandibular condyle.

Although GH stimulates overall growth, it has more profound effects on cartilage growth, which is mediated by insulin-like growth factor I (IGF-I) (Isaksson *et al.*, 1987). Cartilaginous growth sites at the cranial base and in the mandible are affected both by a lack and by an excess of GH (Pirinen *et al.*, 1994). GH treatment in girls with Turner's syndrome has been reported to lead only to an increase in length of the ramus of the mandible (Rongen-Westerlaken *et al.*, 1993). However, in that study group, the spheno-occipital synchondrosis was already closed in most cases, and—in contrast to the mature condyle—a synchondrosis that is closed by ossification cannot be re-activated by GH administration (Ranly, 1988).

The anterior cranial base length increased almost significantly ($p = 0.051$) during GH therapy, because the anterior cranial base has its highest rate of growth during the first 2 yrs of life (Ohtsuki *et al.*, 1982). Since the major part of the treated group is already older than 2 yrs, the growth potential of this part of the cranial base has already become very low.

The younger the child at start of GH treatment, the greater the craniofacial growth-promoting effect of GH. This was especially the case for the total cranial base length, the posterior cranial base length, the mandibular corpus length, and the overall mandibular length. This can be explained by Buschang's hypothesis of a craniofacial growth maturity gradient: "The younger the child when the GH treatment is started, the greater the residual growth potential and the greater the growth-promoting effect of the GH therapy" (Buschang *et al.*, 1983). This age-dependent effect is also observed for overall growth of SGA children receiving GH (de Zegher *et al.*, 1996b).

Although there was significant craniofacial catch-up growth in all the treated children and in none of the untreated, most of the treated children in our study group still failed to normalize facial dimensions after 2 yrs of GH therapy. This statistical finding is contrary to the prediction for some variables, as can be seen in Figs. 2 and 3. These Figs. show the predicted average development for the different dose groups. It should be noted, however, that results may be strongly influenced by individual observations in small samples. For example, in our group, one child from the 0.3 treatment group showed a pronounced clockwise facial growth at the start of the study, and the predicted averages concerning the anterior total facial height were certainly influenced by his data.

The GH dose-dependent increase of the SNB angle was not associated with a dose-dependent change in the ANB angle. This could be explained by the fact that the nasion comes forward and downward during growth, and point A is strongly influenced by the eruption of upper central incisors and is sometimes difficult to interpret.

It must be stressed that SGA children comprise a heterogeneous group with different craniofacial growth patterns (Table 2), and that high doses (at least 2 or 3 times the substitution dose) of GH are used to obtain a growth-promoting effect. We cannot exclude the possibility that initial clockwise craniofacial growth might become worse during GH therapy, or that initially normal growth patterns might result in undesirable craniofacial growth patterns at a later age. During the short observation time of this study (2 yrs), none of these potential undesirable developments was observed. Therefore, during GH treatment, catch-up growth occurs toward a normalization without apparent signs of disproportional growth. The long-term effects of this therapy on the craniofacial complex remain to be established.

In conclusion, short SGA children appear to have a growth delay in linear craniofacial dimensions and to have normal angular relationships. High-dose GH treatment for 2 yrs in pre-pubertal SGA children results in overall craniofacial catch-up growth, which is most pronounced in regions with interstitial cartilage growth.

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